Case Report

A forgotten alternative: Bromides for refractory status epilepticus

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Abstract. We present the cases of a 1-month-old infant diagnosed as having malignant migrating partial epilepsy of infancy and a 2-month-old infant with Ohtahara syndrome, who both presented with severe refractory status epilepticus and were treated with potassium bromide when all other antiepileptic drugs failed. Appropriate augmentation of the dosage of potassium bromide led to reduction in the frequency and duration of seizures in both patients. There was a notable reduction in the occurrence of epileptic seizures in both cases, with no apparent side effects. Potassium bromide was of significant benefit for seizure reduction in two infants with intractable seizures. It could be used safely and within a short period. Potassium bromide should be considered as a relatively safe therapeutic option for infants and children with severe intractable seizures when other antiepileptic drugs fail to control the seizures.

Keywords: Bromides, refractory status epilepticus, pediatric intensive care unit, antiepileptic drugs, seizure control, side effects

1. Introduction

Status epilepticus is defined by the International Classification of Epileptic Seizures as a seizure that lasts for a given length of time (30 min or longer in most studies) or is repeated so frequently that the individual does not regain full consciousness between seizures [1]. Refractory status epilepticus is a medical emergency that often requires prompt intervention in the setting of a pediatric intensive care unit (PICU). The term is generally applied to epileptic disorders with continuous seizures or with very little time for recovery between seizures that do not respond to first

or second-line antiepileptic agents [2]. The severe side effects of antiepileptic drugs (AEDs) (clonazepam, midazolam, phenobarbital, valproic acid, topiramate, and others) and their inability to control seizures are well documented. There are situations in epileptic encephalopathies of infancy when seizures are so frequent that they can be described as status epilepticus. These seizures are refractory to all known AEDs, and so their treatment usually involves the use of deep sedation with midazolam and barbiturates in high doses. Tapering of medications returns the infant to the pre-treatment state [3]. Potassium bromide (KBr) is a good therapeutic option for this severe intractable condition due to the relatively rapid control of seizures without the need for mechanical ventilation, leading to a shorter hospitalization stay and a reduced need for multiple AEDs [4,5].

The existing evidence shows that there are good therapeutic results with the administration of KBr, but

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the available data is fairly limited when compared with the extensive data available on other AEDs [4–13]. We now report the results of KBr administration in two female infants who had received combined AEDs protocols that failed to resolve their severe refractory seizures, requiring their admission to the PICU.

2. Case reports

2.1. Case 1

A 1-month-old female infant presented with daily severe partial complex seizures with tonic and cyanotic components. No lesions were revealed on brain magnetic resonance imaging, and the metabolic workup was normal. Her electroencephalogram (EEG) demonstrated electrical activity originating from multiple independent cortical sites, with a similar ictal pattern of rhythmic alpha/theta activity and an increasing involvement of the cortical surface area, and she was diagnosed as having malignant migrating partial epilepsy of infancy. She was admitted to the PICU due to aspiration pneumonia associated with her neurological condition and was tracheally intubated due to severe respiratory failure. Prior to admission in the PICU, she had been treated with phenobarbital, valproic acid and topiramate in therapeutic dosages, all of which failed to reduce the number and severity of the seizures. The seizures were also refractory to benzodiazepines. There was no improvement in the severity of her seizures after she received midazolam, vigabatrin, carbamazepine, propofol, topiramate, hydantoin, and zonisamide in various combinations. KBr was initiated orally at a minimal dosage (20 mg/kg), together with high-dose midazolam (2 mg/kg). A decline in frequency and severity of seizures was first observed after the initial dosage 3 d later. Following a slight improvement in her condition, the KBr dosage was augmented on a daily basis, and she was monitored clinically and by Video EEG for 2 wk until a maximum dosage of 80 mg/kg had been reached. There was a reduction of the seizures approximately one week after KBr treatment onset, with significant clinical improvement (reduction of more than 90% in seizure frequency) after 20 d of bromide therapy. There were no notable side effects. The infant was discharged from the PICU in stable condition with daily short infrequent seizures, but there was no improvement in her alertness or developmental status. She was prescribed a maintenance KBr dosage of 80 mg/kg. Bromides blood levels on discharge were measured at 196 mg/L. An EEG performed several days

following the initiation of the KBr treatment showed modified hypsarrhythmia, similar to previous EEGs, despite KBr treatment.

2.2. Case 2

A 2-month-old female infant diagnosed as having Ohtahara syndrome was resuscitated immediately after birth due to placenta abruption. She had been experiencing epileptic seizures from birth, with tonic posturing and prolonged apneas leading to desaturations. An EEG performed a few days after birth demonstrated a pattern of suppression-burst with high-voltage paroxysmal discharges separated by prolonged periods of nearly flat tracing. A brain magnetic resonance imaging showed no signs of cerebral pathology. The infant was admitted to the PICU with severe seizures, apnea, inability to maintain oxygen saturation and bradycardia. She was diagnosed as having pneumonia, and intubated due to severe respiratory failure. Phenobarbital, valproic acid, topiramate, midazolam, clonazepam and zonisamide had little effect in controlling her seizures. KBr was then initiated orally at a low dosage (20 mg/kg) with first signs of clinical improvement seen after 5 d. Daily evaluation of the clinical findings along with Video EEGs led to daily augmentation of the dosage for 10 d until it reached 40 mg/kg twice a day. KBr was used in various combinations with valproic acid, phenobarbital, clonazepam and zonisamide, and there was a reduction in both the quality and quantity of her seizures approximately 10 d from KBr treatment onset. Further clinical improvement was noted despite discontinuation of most AEDs. There were no notable side effects. The infant was released in a stable condition with less alarming seizures and no need for mechanical ventilation. Maintenance treatment consisted of a combination of KBr (40 mg/kg twice a day) and clonazepam (0.5 mg/kg twice a day). Bromides blood levels were measured on discharge and were found to be 110 mg/L. Despite the significant reductions in the amplitude, duration and frequency of her seizures, she continued to experience periodic seizures after her release. Comprehensive diagnostic efforts failed to identify an etiology for those seizures.

3. Discussion

In early-onset epileptic encephalopathies, seizure frequency can reach a level that can be described as status epilepticus, which can be so severe as to be life threatening.

Affected children are often admitted to the PICU. Patients with epilepsy are usually maintained satisfactorily on various AEDs [3]. In infantile epileptic encephalopathies, however, the epilepsy is so severe that it does not respond to traditional AEDs. The resistance to traditional AEDs is also commonly seen in older children, thus early therapeutic dosage of KBr is often worthwhile [4].

KBr was the first drug ever used for treating epileptic disorders, with clinical data dating back to 1857 [14]. It was later abandoned as an AED mainly due to the increasing usage of phenobarbitone. In the 1980's, the usage of KBr was reported in a few articles, mainly in Germany and Japan [4,5,10–13]. Germany is currently the only country in which the drug is registered and approved for use (Dibro-Be mono®). It is indicated for primary and secondary generalized tonic-clonic seizures in early childhood, grand mal seizures and severe myoclonic syndromes [15].

KBr is a water soluble salt, consumed orally, and absorbed almost completely in the upper gastrointestinal tract, distributing in the extracellular space. The mechanism by which KBr produces anticonvulsant effects is unknown, but the resulting potentiating gamma-aminobutyric acidergic inhibition appears to be consistent with the anticonvulsant effect of the drug and with the enhanced paired-pulse inhibition of evoked field potentials. Therefore, it was suggested that KBr compounds increase gamma-aminobutyric acid inhibition by which they control epileptic seizures [15].

A review of the literature yielded a number of side effects, mainly affecting the central nervous system, gastrointestinal tract, and the skin. Side effects included acne, loss of appetite and weight, and fatigue, sedation, ataxia [11]. Severe side effects presented as anorexia in bromide intoxication, apathy, and developmental regression [16].

Bromides were suggested as an effective alternative treatment in several types of epileptic disorders. Lotte et al. [12] described a good response to KBr therapy in 32 patients suffering from Dravet syndrome with a specific mutation in the SCN1A gene, and notable reduction in seizures over a period longer than 3 months. Other notable studies include Tanabe et al. [13] that included a national survey in Japan that exemplified the effectiveness of KBr in the treatment of severe myoclonic epilepsy in infancy. There are also some case reports on the alternative use of KBr that demonstrated its effectiveness in reducing the number of seizures and, in some cases, resulting in their complete cessation [6–9]. Takayanagi et al. [6] described two infants treated

with daily doses of KBr for convulsive focal motor seizures with unconsciousness and focal motor seizure status. The treatment resulted in complete cessation of the attacks. Another report from Takusa et al. [7] described a 5-year-old boy with a peculiar type of post-encephalitic/encephalopathic epilepsy treated first with high-dose phenobarbital therapy that controlled the convulsions, but was discontinued because of drug-induced aplastic anemia. Alternative bromide therapy was markedly effective in controlling his seizures. Okuda et al. [8] described two infants diagnosed with malignant migrating partial seizures in infancy who were treated successfully with potassium bromide after conventional AEDs failed to control the seizures. More recent case reports by Fasulo et al. [17] and Djuric et al. [18] on the therapeutic advantages of bromides in malignant migrating partial seizures described an almost complete cessation of seizures in infants suffering from malignant migrating partial seizures.

The collective experience with KBr is limited to pediatric centers specializing in epilepsy, and there are no reports on the use of KBr as an alternative antiepileptic agent in the setting of a PICU. Infants suffering from severe status epilepticus are prone to severe complications of their neurological condition [3] and frequently need to be treated in intensive care unit facilities. Due to the nature of the seizures, hospitalization can be prolonged in duration. Moreover, the risk of neurologic complications is high.

In conclusions, we recommend that KBr should be considered as a tertiary therapeutic option, in combination with other AEDs, for the management of severe, refractory status epilepticus. Our clinical experience suggests that KBr has a relatively rapid effect on the severity and frequency of refractory seizures. Although the length of our experience is limited, it is our impression that the benefit of using KBr in refractory cases outweighs its side effects, especially in severe cases that require intensive care unit care.

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